REMARKS

Claims 1 to 6 and 18 to 47 are pending. Claims 1, 3, and 5 have been amended and new claims 18 to 47 have been added. The compounds recited in claims 1 and 5 are now specified to be a peptide, peptidomimetic, small organic molecule or small inorganic molecule. The compounds recited in claim 3 are specified to be a peptidomimetic, a small organic molecule, or a small inorganic molecule. These amendments add no new matter. In particular, the amendments to claims 1, 3, and 5 are supported in the application, e.g., at page 13, line 25-page 14, line 7.

New claims 18-20 depend from claim 1 and are drawn to specific types of peptides. Support for new claims 18-20 is found, e.g., at page 13, line 25-page 14, line 7. New claims 21-36, and 45 to 47 are drawn to methods of identifying compounds that modulate JNK3 expression, activity, binding, or phosphorylation of a JNK3 substrate that include an assay for excitotoxicity of the compound. Claims 37-40 are drawn to a method of identifying a compound using an excitotoxicity assay. Support for new claims 21-40 and 45-47 are found throughout the specification, e.g., at page 22, line 1-page 23, line 3, and in Examples 3-8. Claims 41-47 are drawn to methods of identifying compounds that decrease JNK3 phosphorylation of a substrate. Support for these claims is found throughout the specification, e.g., in Examples 5 and 9. Thus, none of the new claims add new matter to this application.

The Invention

Applicants discovered that mice lacking the JNK3 gene (a gene encoding a c-Jun N-terminal kinase) develop normally and are resistant to excitotoxic damage. The invention relates to methods of identifying compounds that modulate JNK3 expression, activity, or binding using *in vitro*, *in vivo*, or combined *in vitro* and *in vivo* techniques.

35 U.S.C. § 102(e)

Claims 1 and 2 have been rejected as being anticipated by U.S. 5,877,309 (McKay). Claim 1 is drawn to a method of identifying a compound that modulates JNK3 expression. The Office Action states, "McKay et al. disclose a method for assaying modulation of expression of a gene encoding a JNK protein including ...JNK3." The Office Action further states that "McKay et al. disclose oligonucleotides capable of hybridizing to nucleic acids encoding JNK1-3 and modulating the expression of JNK proteins" (Office Action at page 3). However, McKay describes the use of only oligonucleotides.

On the other hand, applicants have amended claim 1 to recite compounds that are peptides, peptidomimetics, small organic molecules, or small inorganic molecules, none of which are oligonucleotides. As a result, applicants submit that McKay does not anticipate amended claim 1. Claim 2 depends from claim 1 and adds that the compound decreases the expression of JNK3. Because claim 2 depends from amended claim 1, it is also not anticipated by McKay. Thus, applicants request that the rejection under 35 U.S.C. § 102 (e) be withdrawn.

35 U.S.C. § 103 (a)

Claims 3 and 4 have been rejected as unpatentable over McKay in view of Chauhan et al. (Blood, 89:227-234, 1997). Claims 3 and 4 are drawn to methods of identifying a compound that modulates JNK3 activity. The Office Action admits that McKay "does not disclose modulation of the activity of JNK3" (at page 3). The Office Action then cites Chauhan for its description of an JNK activity assay to examine the effects of IL-6 on multiple myeloma cells. However, the Office Action concedes that Chauhan "does not teach specifically a method for assaying for modulators of the activity of JNK3." Nevertheless, the Office Action asserts that it would have been obvious for one skilled in the art to combine the information in the two references to develop a method of identifying modulators of JNK3 activity. Applicants respectfully disagree for the following reasons.

Applicants have amended claim 3 to state that the compound is a peptidomimetic, a small organic molecule, or a small inorganic molecule. As discussed above, McKay discloses compounds that are oligonucleotides, but does not disclose the use of any other compounds. Chauhan et al. describes only the use of IL-6, a polypeptide. Thus, the addition of Chauhan et al. to McKay cannot make obvious amended claim 3, and its dependent claim 4.

Applicants also point out that contrary to the assertion in the Office Action that Chauhan et al. appears to have included all JNK isoforms, there is no evidence that Chauhan et al. assayed JNK3. In fact, since Chauhan et al. use multiple myeloma cells and JNK3 is expressed primarily in nervous tissue and testis, there is no reason to expect that Chauhan et al. detected JNK3.

Next, the Examiner has rejected claims 5 and 6 as allegedly unpatentable over Gupta et al. and McKay. Claims 5 and 6 are drawn to methods of identifying a compound that binds to JNK3. Claim 6 depends from claim 5. As stated in the Office Action (at page 5), "Gupta et al. does not teach identification of compounds that modulate the binding of JNK3 to its substrate." However, the Office Action concludes that it would have been obvious to those skilled in this art to use the information in Gupta to develop a method for identifying a compound that inhibits the binding reaction of JNK3 with a substrate. Applicants respectfully disagree for the following reasons.

Claim 5 has been amended to state that the test compound is a peptide, a peptidomimetic, a small organic molecule, or a small inorganic molecule. As discussed above, McKay discloses the use of oligonucleotides, but does not disclose the use of any other compounds. As stated in the Office Action, "Gupta et al. does not teach identification of compounds that modulate the binding of JNK3 to its substrate" (at page 5). Thus, the addition of Gupta et al. to McKay at best might suggest a method of identifying oligonucleotides that modulate the binding of JNK3 to a substrate. However, this does not render amended claim 5 and dependent claim 6 obvious.

In view of the amendments to claims 3 and 5, and the arguments presented above, applicants request the withdrawal of the alleged obviousness rejections of claims 3 to 6.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made." Filed herewith is a check in payment of the excess claims fees required by the above amendments and Petition for Automatic Extension with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket no. 10363-005001.

Respectfully submitted,

Date: 3-12-01

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Version with Markings to Show Changes Made

1. (Amended) A method of identifying a compound that modulates JNK3 expression, the method comprising:

incubating a cell that can express a JNK3 protein with a compound under conditions and for a time sufficient for the cell to express a JNK3 protein absent the compound, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, or a small inorganic molecule;

incubating a control cell under the same conditions and for the same time absent the compound;

measuring JNK3 expression in the cell in the presence of the compound;

measuring JNK3 expression in the control cell; and

comparing the amount of JNK3 expression in the presence and absence of the compound, wherein a difference in the level of expression indicates that the compound modulates JNK3 expression.

2. The method of claim 1, wherein the compound decreases the expression of JNK3.

3. (Amended) A method of identifying a compound that modulates JNK3 activity, the method comprising:

incubating a cell that has JNK3 activity with a compound under conditions and for a time sufficient for the cell to express JNK3 activity absent the compound, wherein the compound is a peptidomimetic, a small organic molecule, or a small inorganic molecule;

incubating a control cell under the same conditions and for the same time absent the compound;

measuring JNK3 activity in the cell in the presence of the compound;

measuring JNK3 activity in the control cell; and

comparing the amount of JNK3 activity in the presence and absence of the compound wherein a difference in the level of activity indicates that the compound modulates JNK3 activity.

4. The method of claim 3, wherein the compound decreases JNK3 activity.

5. (Amended) A method of identifying a compound that modulates the binding of a JNK3 polypeptide to a substrate, [said] the method comprising comparing the amount of a JNK3 polypeptide bound to a substrate in the presence and absence of a selected compound, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, or a small inorganic molecule, wherein a difference in the amount of binding of a JNK3 polypeptide to a substrate indicates that [said] the selected compound modulates the binding of a JNK3 polypeptide.

6. The method of claim 5, wherein the binding of a JNK3 polypeptide to a substrate is decreased.

Add new claims 18 to 47 as follows.

18. (New) The method of claim 1, wherein the compound is a soluble peptide.

19. (New) The method of claim 1, wherein the compound is a phosphopeptide.

20. (New) The method of claim 3, wherein the compound is a peptidomimetic.

21. (New) The method of claim 5, wherein the compound is a soluble peptide.

22. (New) The method of claim 5, wherein the compound is a phosphopeptide.

23. (New) A method of identifying a compound that modulates JNK3 expression, the method comprising:

incubating a cell that can express a JNK3 protein with a compound under conditions and for a time sufficient for the cell to express a JNK3 protein absent the compound;

incubating a control cell under the same conditions and for the same time absent the compound;

measuring JNK3 expression in the cell in the presence of the compound;

measuring JNK3 expression in the control cell;

comparing the amount of JNK3 expression in the presence and absence of the compound;

selecting the compound if there is a difference in the level of expression in the presence and absence of the compound; and

administering the selected compound to an animal model of an excitotoxic disorder and assaying the animal for excitotoxicity,

wherein a decrease in excitotoxicity in the animal indicates that the compound modulates JNK3 expression.

24. (New) The method of claim 23, wherein the compound decreases the expression of JNK3.

25. (New) The method of claim 23, wherein the animal model is a mouse model.

26. (New) The method of claim 23, wherein the excitotoxic disorder is kainic acid-induced or pentetrazole-induced.

27. (New) A method of identifying a compound that modulates JNK3 activity, the method comprising:

incubating a cell that exhibits JNK3 activity with a compound under conditions and for a time sufficient for the cell to exhibit JNK3 activity absent the compound;

incubating a control cell under the same conditions and for the same time absent the compound;

measuring JNK3 activity in the cell in the presence of the compound;

measuring JNK3 activity in the control cell;

comparing the amount of JNK3 activity in the presence and absence of the compound;

selecting the compound if there is a difference in the level of activity in the presence and absence of the compound; and

administering the selected compound to an animal model of an excitotoxic disorder and assaying the animal for excitotoxicity, wherein a decrease in excitoxicity in the animal indicates that the compound modulates JNK3 activity.

28. (New) The method of claim 27, wherein the animal model is a mouse model.

29. (New) The method of claim 27, wherein the excitotoxic disorder is kainic acid-induced or pentetrazole-induced.

30. (New) The method of claim 27, wherein the compound decreases JNK3 activity.

31. (New) The method of claim 27, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, a small inorganic molecule, or an oligonucleotide.

32. (New) A method of identifying a compound that modulates the binding of a JNK3 polypeptide to a substrate, the method comprising:

comparing the amount of a JNK3 polypeptide bound to a substrate in the presence and absence of a compound;

selecting the compound if there is a difference in the amount of JNK3 polypeptide bound to the substrate in the presence and absence of the compound; and

administering the selected compound to an animal model of an excitotoxic disorder and assaying the animal for excitotoxicity,

wherein a decrease in excitotoxicity in the animal indicates that the selected compound modulates the binding of a JNK3 polypeptide to the substrate.

33. (New) The method of claim 32, wherein the animal model is a mouse model.

34. (New) The method of claim 32, wherein the excitotoxic disorder is kainic acid-induced or pentetrazole-induced.

35. (New) The method of claim 32, wherein the binding of a JNK3 polypeptide to a substrate is decreased.

36. (New) The method of claim 32, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, a small inorganic molecule, or an oligonucleotide.

37. (New) A method of identifying a compound that modulates JNK3- mediated excitotoxicity, the method comprising

administering a test compound to an animal model of an excitotoxic disorder; and

assaying the animal for excitotoxic effects, wherein a decrease in excitotoxic effects in the presence of the test compound compared to an untreated control indicates that the compound modulates JNK3 excitotoxicity.

38. (New) The method of claim 37, wherein the animal model is a mouse model.

39. (New) The method of claim 37, wherein the excitotoxic disorder is kainic acid-induced or pentetrazole-induced.

40. (New) The method of claim 37, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, a small inorganic molecule, or an oligonucleotide.

41. (New) A method of identifying a compound that inhibits JNK3 phosphorylation of a substrate, the method comprising comparing the phosphorylation of a JNK3 substrate in the presence and absence of a selected compound, wherein a decrease in the phosphorylation of the JNK3 substrate indicates that the selected compound inhibits JNK3 phosphorylation of the substrate.

42. (New) The method of claim 41, wherein the JNK3 substrate is c-Jun.

43. (New) The method of claim 41, wherein the JNK3 and the substrate are in a cell.

44. (New) The method of claim 41, wherein the JNK3 and the substrate are in solution.

45. (New) 45. The method of claim 41, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, or a small inorganic molecule.

46. (New) A method of identifying a compound that inhibits phosphorylation of a JNK3 substrate, the method comprising:

comparing the amount of a JNK3 substrate phosphorylated in the presence and absence of a compound;

selecting the compound if there is a decrease in the amount of JNK3 substrate phosphorylation in the presence compared to the absence of the compound; and

administering the selected compound to an animal model of an excitotoxic disorder and assaying the animal for excitotoxicity,

wherein a decrease in excitotoxicity in the animal indicates that the selected compound inhibits the phosphorylation of a JNK3 substrate.

47. (New) The method of claim 46, wherein the JNK3 substrate is c-Jun.